Statistical analysis plan (SAP) for MEDIC2

The combined efficacy of a 12-week treatment program of neuromuscular exercise, patient education, diet, insoles and medicine as treatment of knee osteoarthritis for patients not eligible for a total knee replacement: a randomized controlled trial

Skou, Søren Thorgaard; Roos, Ewa M.; Laursen, Mogens Berg; Rathleff, Michael Skovdal; Arendt-Nielsen, Lars; Simonsen, Ole; Rasmussen, Sten

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STATISTICAL ANALYSIS PLAN (SAP) FOR:

The combined efficacy of a 12-week treatment program of neuromuscular exercise, patient education, diet, insoles and medicine as treatment of knee osteoarthritis for patients not eligible for a total knee replacement: a randomized controlled trial

Study chair:
Søren Thorgaard Skou, PhD-student[1,2] (Principal investigator, Corresponding author)
Ewa M Roos, PhD, Professor[3]
Mogens Berg Laursen, MD, PhD[1]
Michael S. Rathleff, PhD[4]
Lars Arendt-Nielsen, DMSc, PhD, Professor[2]
Ole Simonsen, MD, DMSc[1]
Sten Rasmussen, MD, Associate Professor[1,2]

Statistical advisor:
Martin Berg Johansen, MSc[5]
Jonas Ranstam, Professor[6]

[1]Orthopaedic Surgery Research Unit, Aalborg University Hospital, Aalborg, Denmark
[2]Department of Health Science and Technology, Centre for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark
[3]Research Unit for Musculoskeletal Function and Physiotherapy, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
[4]Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Aalborg, Denmark
[5]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[6]Lund University and Skane University Hospital, Lund, Sweden

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1. Study Synopsis

Knee osteoarthritis (OA) is a major cause of chronic pain and a leading cause of functional disability in the elderly [1]. Patient education, exercise and weight loss are recommended as first line treatment, with insoles and medicine as additional treatment modalities [2, 3].
However, the combined efficacy of these non-surgical treatments remains unknown. This randomized, controlled trial aims at investigating whether a 12-week non-surgical treatment program (the MEDIC-treatment; neuromuscular exercise, patient education, weight loss (if needed), insoles and medicine) results in greater improvement in quality of life, pain and function compared to usual care (two information leaflets containing information on knee OA and advice regarding the recommended treatments) in patients with knee OA not eligible for a total knee replacement (TKA) (Figure 1).

2. Study Objectives and Outcomes

A study protocol elaborating the methods used in this study has been published [4]. All outcomes were obtained from all participants at baseline and all follow-ups (3months, 6months and 12months; Figure 1). The 12month follow-up is expected to be finalized in August 2014.

2.1. Primary Objective and Outcome

The primary objective is to compare change from baseline to the 1 year follow-up (including all follow-ups) between patients randomized to the MEDIC-treatment or usual care in the average score of four of the five subscales from the Knee Injury and Osteoarthritis Outcome Score ($KOOS_4$) covering pain, symptoms, activities of daily living (ADL), and knee-related quality of life (QOL).

An overall KOOS-score can be used as primary endpoint in an RCT, if defined *a priori* [5]. However, the purpose of an overall score ($KOOS_4$) as the primary endpoint is to avoid issues with multiplicity. Since an overall score has not been subjected to psychometric validation the individual KOOS subscales must be analyzed as secondary outcomes to enable clinical interpretation of the contributions of the individual subscales to the overall $KOOS_4$ score [5].

The reason for not including the KOOS subscale Sports & recreation function (Sport/Rec) in the primary endpoint $KOOS_4$ was that it was expected that a large proportion of the participants in this study would not perform the activities assessed in this subscales (running, jumping, squatting, kneeling and pivoting). This could potentially affect the content validity, which is why it was excluded from the aggregated primary outcome.

Each item in KOOS is scored from 0-4 on a Likert scale. Subscale scores are given separately (see www.koos.nu for user's guide and scoring) ranging from 0 [worst] to 100 [best]. KOOS has previously been validated for patients eligible for TKA [6, 7]. Each subscale of the primary outcome of this study, $KOOS_4$, will be calculated according to the instructions in the user's

guide. After that an average of the four subscales will be calculated giving each subscale equally large impact on the $KOOS_4$ score using this formula:

$KOOS_4$ = (KOOS Pain + KOOS Symptoms + KOOS ADL + KOOS QOL)/4

2.2. Secondary Objectives and Outcomes

The secondary objectives are to compare change from baseline to the 1 year follow-up (including all follow-ups) between groups in a range of outcomes. These outcomes will only be supportive, explanatory and/or hypothesis generating, which is why multiplicity is not considered to be a problem[8].

The outcomes are (arranged hierarchically according to their importance):

1) The five subscales of KOOS:
    a. Symptoms
    b. Pain
    c. ADL
    d. Sport/Rec
    e. QOL
2) Functional performance
    a. Time from the Timed Up and Go [10]
    b. Time from the 20-meter walk test [11]
3) The descriptive system (EQ-5D Index) and the EQ VAS (0-100) from the Euro-Quality-of-Life – 5 Dimensional form (EQ-5D-3L) [9].
4) Weight change in percent measured without shoes at the same time of day and on the same scale (seca 813, seca gmbh & co. kg., Hamburg, Germany)
5) Usage of pain killers during the last week (yes/no), number of weekly paracetamols (1g) and ibuprofen (400mg) and other NSAIDs.
6) Adverse events (AE) and seriously adverse events (SAE) will be registered in three ways and divided into index knee or sites other than index knee. The project physiotherapist will record any adverse events that the participant experiences or tells them about. For the participant having a TKA, a project worker will look through hospital records to register if any pre-defined perioperative and postoperative adverse events occurred. At all follow-ups, the assessor will use open-probe questioning to assess adverse events in all participants (Table 1).

2.3. Exploratory Objectives

The exploratory objectives are to compare change from baseline to the 1 year follow-up (including all follow-ups) between groups in a range of outcomes. These outcomes will only be exploratory and/or hypothesis generating, which is why multiplicity is not considered to be a problem [8].

The outcomes are:

1) Pain intensities on a 100 mm VAS with terminal descriptors of 'no pain' and 'worst pain possible' in the following situations: at rest, at night, after 50 m of walking, after 30 min. of walking, after exercise/physical activity, during preferred physical activity, and worst pain and least pain in the previous 24 hours.

2) Number of sites with pain in the previous 24 hours shaded on a region-divided body chart

3) Pain location and type assessed using the reliable interviewer-administered questionnaire Knee Pain Map [12].

4) Maximum isometric muscle strength (converted to Nm using the length of the lower leg) measured bilaterally in knee flexion and knee extension in a make test using a handheld dynamometer (Powertrack II^{TM} Commander from JTech Medical Industries, Salt Lake City, Utah, USA).

5) Pressure pain thresholds measured bilaterally using a handheld algometer (Algometer Type II, Somedic AB, Hoerby, Sweden)) at five sites at the knee and the m. tibialis anterior muscle and the m. extensor carpi radialis longus [13].

6) Postural balance assessed using an instrumented force platform (Good Balance, Metitur Oy, Jyvaskyla, Finland), measuring the centre of pressure (COP) excursion of the participants (100Hz).

7) Self-efficacy in improving pain, function and QOL in various situations using a 100 mm VAS with terminal descriptors of 'very unsure' and 'very sure'.

Additionally, a within-group analysis will be conducted to investigate if treatment compliance (se section 2.5.) is associated with the change in $KOOS_4$.

Based on recent studies in similar patient populations [14, 15], an exploratory analysis applying a 15% difference in change in $KOOS_4$ between groups from baseline to the 1 year follow-up as the Minimal Important Change (MIC; see section 2.6.) will be conducted.

An analysis of Number Needed to Treat (NNT) will be performed. NNT estimates the number of people who would need to go through the MEDIC-treatment for one person to have a MIC (15%) in $KOOS_4$ from baseline to the 12 month follow-up compared to the usual care group.

Furthermore changes in the following exploratory outcomes from baseline to 3 months will be compared between groups to investigate the effects on pain sensitization: 1), 2), 3), and 5).

The test setup for muscle strength and pressure pain thresholds will be assessed in a study of test-retest reliability of 20 knee OA patients.

Further exploratory objectives may be added later on.

2.4. Economic Evaluation

The EQ-5D will be applied in a health economic evaluation [9].

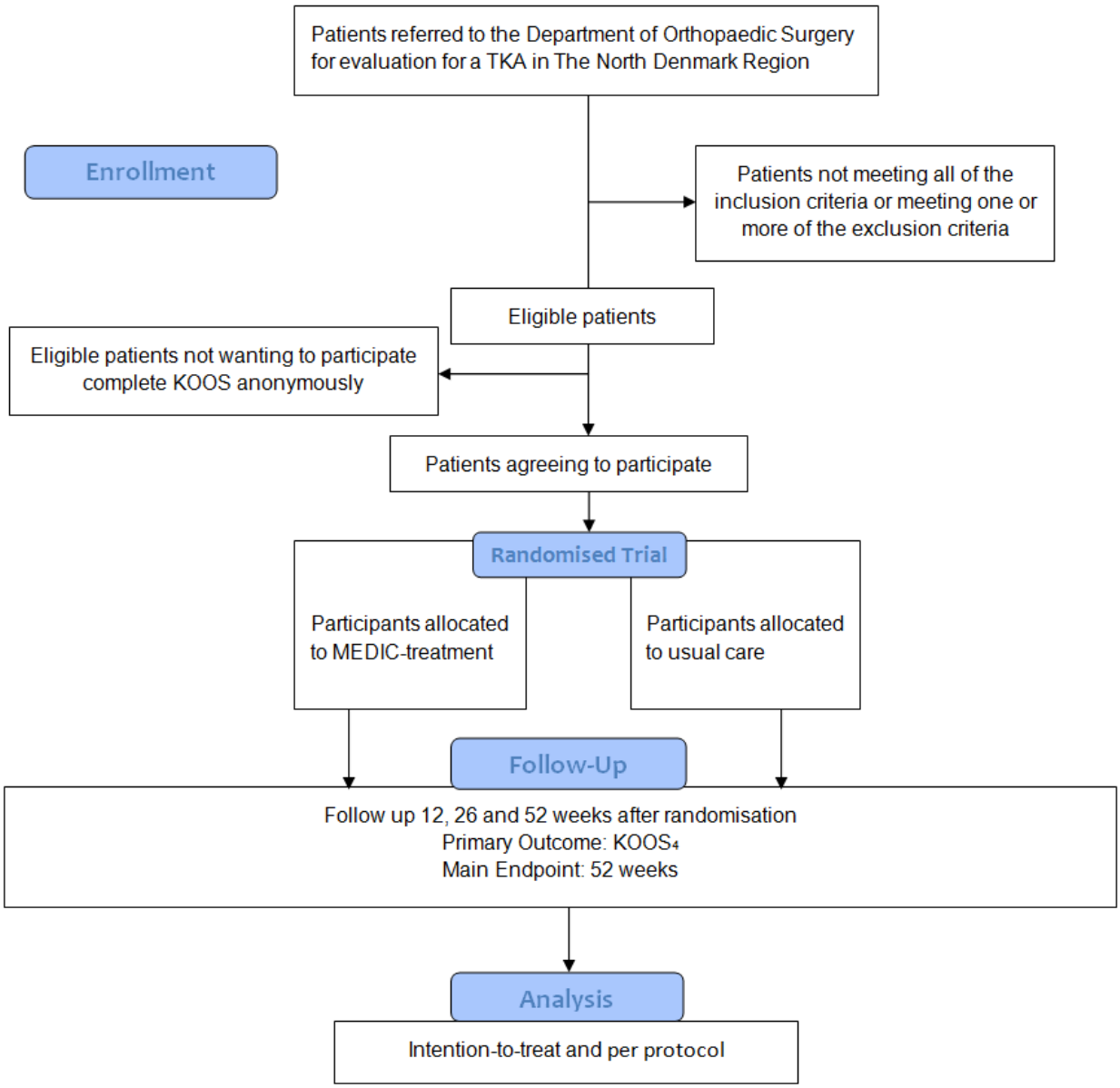

Figure 1: Flow chart

2.5. Descriptive Outcomes

Baseline characteristics will be presented in a table (Table 2).

Furthermore, the following treatment-related variables will be presented descriptively:

1) Compliance with exercise will be recorded by the physiotherapist during the 12 weeks. Compliance is assessed as the total number of exercise sessions completed out of the total 24 sessions (two sessions a week over twelve weeks). Good compliance is defined as participation in 75 % or more of the exercise sessions, moderate compliance as participation in 50-74 % of the sessions and poor compliance as participation in less than 50 % of the sessions.
2) Compliance with insoles, patient education and dietary advice will be assessed at each follow-up, using a five-point scale assessing the adherence to the treatment (never, every month, every week, every day, all the time).
3) Satisfication with the treatment effect will be registered at each follow-up on a five-point Likert scale (very dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied, very satisfied). Surgery during the 12 month follow-up period will also be registered (Table 3).

2.6. Specification of endpoints

2.6.1. Primary Endpoint

The primary outcome ($KOOS_4$) will be analyzed in intent-to-treat (ITT) and per-protocol (PP) analyses (see section 5.1.).

The ITT population will be defined as those randomized to the two treatment arms.

The PP population will be defined as those who stayed in the treatment arm allocated by randomization during the 1 year period and those who were randomized to the MEDIC-treatment and had at least 75% compliance with the exercise during the 12 week intervention period. This means that the following will be excluded from the PP analysis:

1) Those who were randomized to the MEDIC-treatment, but did not participate in at least 75% of the exercise sessions and/or did not participate in the other aspects of the MEDIC-treatment; and

2) Those who were randomized to treatment according to the MEDIC-treatment or to usual care but had an TKA during the 1 year period

Treatment effect will be determined as change in the primary outcome $KOOS_4$ from baseline to the 1 year follow-up.

The trial is designed as a superiority trial, i.e. we expect that the group allocated to the MEDIC-treatment will improve at least 10 points more than the group allocated to usual care in the primary outcome $KOOS_4$ and the individual KOOS subscales from baseline to the primary endpoint after 1 year.

Since KOOS contains the full and original version of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), it has been suggested to apply a MIC of 10 points, which has been demonstrated for WOMAC[16]. Recent studies in similar patient populations [14, 15]

have applied a MIC of 15%. However, percentage change from baseline is not recommended as an outcome in controlled trials, since it has low statistical power, is highly sensitive to changes in variance and fails to protect from bias in the case of baseline imbalance [17]. We acknowledge that MIC is dependent on context factors such as population, intervention, and time to follow-up[18], which is why we will conduct an exploratory analysis applying a 15% difference in change in $KOOS_4$ and the individual KOOS subscales between groups from baseline to the 1 year follow-up as the MIC.

Based on the mentioned shortcoming with percent change as the outcome in controlled trials, we decided to maintain the 10 point MIC in $KOOS_4$ and the individual KOOS subscales in this study. Therefore, the sample size calculation was based on 90% power to detect a 10 point difference between groups in $KOOS_4$ after 1 year, which will be used to define the superiority margin (Δ=10points).

Superiority will be tested using the two-sided 95% confidence interval (CI) of the mean change in $KOOS_4$ between the two treatment groups. Treatment according to the MEDIC-treatment will be considered superior to usual care when the lower side of this 95% CI excludes the superiority margin (Δ).

2.6.2. Secondary Endpoints

Secondary endpoints will be analyzed for between group differences using ITT and PP analyses (see section 5.2.).

Each subscale of the KOOS will be presented graphically for its development over the 1 year period. Statistical analyses will be made to assess between groups differences from baseline to 1 year for each subscale.

Each subscale of the KOOS, time (s) in Timed Up and Go, time (s) in 20-meter walk test, EQ-5D Index, EQ VAS, weight (kg) and self-efficacy will be presented as mean (95% CI) for each treatment group, while usage of pain killers will be presented as actual numbers and proportions. Between group differences in change from baseline to 1 year will be statistically assessed. The analysis for weight will only be conducted for participants with BMI$\geq$25.

All issues during the trial found in the treatment records from the project physiotherapist, hospital records or the questionnaire from the follow-ups will be assessed to determine whether it represents an AE or not. AE will be presented in a table (see Table 1) and analyzed statistically by comparing actual numbers of serious AE (site other than index knee, index knee and all serious events) and non-serious AE (site other than index knee, index knee and all serious events).

3. Study Design

3.1. Sample Size

We used a common between-subject standard deviation of 14 to calculate the sample size needed to detect a 10 point difference in $KOOS_4$ and the individual KOOS subscales (power of 90 % and significance level at 0.05 (twosided)). The calculations showed that 41 participants were required in each group.

To account for crossover to TKA during follow-up and missing data, the drop-out rate was set to 20 % and therefore, a total of 100 participants were randomized.

3.2. Randomization and Blinding

The schedule for randomization was randomly generated using a computer before the initiation of the trial. The randomization was by random permuted blocks, stratified according to the clinic (Frederikshavn or Farsoe) to control for variation in patient characteristics in the two clinics. To conceal the outcomes of the randomization, the allocation numbers were put in concealed, opaque C5 envelopes. In blocks of eight, these envelopes were placed in consecutively numbered opaque larger envelopes (seven larger envelopes in total for each clinic). An independent staff member prepared the envelopes. These were kept in a locked location accessible only by one research assistant at each of the respective clinics. Following the informed consent and completion of the baseline measures, a smaller envelope from the numbered larger envelopes was opened by the research assistant and the allocation revealed to the participant. When only two smaller envelopes were left in the first of the numbered larger envelopes, the smaller envelopes of the second larger envelope were added. When there were six smaller envelopes left in the sixth of the numbered larger envelopes at each clinic, the last two of the smaller envelopes were added.

The outcome assessor is blinded to group allocation, is not involved in providing the interventions, and is unaffiliated with the treatment sites. The participants and the project physiotherapist delivering part of the interventions could not be blinded. The statistician performing the statistical analyses will be blinded to group allocation.

The writing committee of this study (identical to the study chair in this SAP) will, prior to breaking the code, conduct two interpretations of the results on the basis of a blinded review of the data from the primary endpoint (changes from treatment A compared to changes from treatment B), one assuming that treatment A is the MEDIC-treatment, and the other assuming that treatment A is usual care. Not until the writing committee has agreed that there will be no further changes in the interpretation the randomization code will broken, ensuring that bias in the interpretation is reduced.

4. Study Population

4.1. Subject Disposition

Study procedures, including recruitment strategies and inclusion and exclusion criteria, have been published previously in a study protocol [4]. Patient included in the trial were randomized to: A) the MEDIC-treatment (Medicine, neuromuscular Exercise, Diet (if needed), Insoles and Cognitive treatment (patient education)) or B) usual care (two information leaflets containing information on knee OA and advice regarding the recommended treatments). No patients fulfilling all eligibility criteria could be excluded.

The frequency of TKA and other surgeries will be registered and reported (Table 3).

5. Statistical Analysis

5.1. Primary Endpoint

The between-group difference in change in $KOOS_4$ from baseline to 1 year follow-up will be the primary outcome, complemented by the individual KOOS subscales assessing pain, symptoms, ADL function and Quality of Life to allow for clinical in-depth interpretation.

Between group comparisons of treatment effect (change in $KOOS_4$ from baseline to 1 year follow-up) will be dependent on data distribution. We expect the change to be normally distributed and analysis will be made using a mixed model ANOVA with subject being a random factor and visit (baseline, 3, 6 and 12 months), treatment arm (TKA + MEDIC, MEDIC) and site (Frederikshavn, Farsoe) being fixed factors. Baseline $KOOS_4$ will be a covariate. Furthermore interactions between the fixed factors will be included in the model. P-values and 95% CI will be presented to assess superiority.

5.2. Secondary Endpoints

Between groups comparisons of the change from baseline to the 1 year follow-up in all secondary endpoint will be handled similar to the primary endpoint.

5.3. Major Protocol Deviations

In the study protocol [4] we decided to apply a generalized estimating equations regression model (GEE) to analyse KOOS to take all follow-ups into account. However, the sample size calculation was based on the change from baseline to 12 months and not the change over several different follow-ups. After consulting with several statisticians, the authors decided to change the method of analyses for all endpoints to a mixed model ANOVA, which is the most suitable method to investigate changes from baseline to 12 months taking baseline values into account. A mixed model ANOVA is conditional (subject-specific opposite to a GEE that is population-

specific)[19] and enables inclusion of the entire full analysis set (defined as an analysis set being as complete and as close to the ITT-principles of including all randomized patients as possible[20]) even with an unbalanced dataset [21]. Furthermore, the authors believe that the application of this method makes the results and the conclusion of the study easier to understand and interpret. Since this SAP is published before any analyses have been performed, the change in method of statistical analyses will not induce any bias.

6. Implementation of Analysis Plan

This SAP will be used as a work description for the statistician performing the analyses. All analyses will be performed by the same statistician and none of the investigators involved in this trial will perform any of the statistical analyses.

The implementation of the SAP will be as follows:

1. A 'data collection form' will be outlined in a collaboration between the database manager, statistician and principal investigator (Søren Thorgaard Skou).

2. The database manager will code each treatment arm into 'treatment A' and 'treatment B' and thus leaving all others blinded from treatment during the analyses.

3. Blinded data will be delivered to the statistician according to the 'data collection form'.

4. Primary, secondary and exploratory endpoint analyses will be made blinded from treatment

5. Results will be presented to the writing committee of the trial (identical to the study chair in this SAP) where any uncertainties will be clarified and blinded interpretations of the primary endpoint results will be conducted prior to unblinding of data.

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8. Tables

8.1. Table 1. Adverse Events

Adverse events	**MEDIC**	**Usual Care**	**P Value**
	Number of events		
Serious events			
Site other than index knee			
Musculoskeletal			
Skin			
Gastrointestinal			
Other			
Index knee			
Pain			
Swelling			
Subjective instability			
Decreased range of motion			
Distortion			
Other			
During surgery			
Postoperatively			
All serious events			
Nonserious events			
Sites other than index knee			
Index knee			
All nonserious events			

8.2. Table 2. Baseline characteristics

Baseline characteristics	**MEDIC**	**Usual Care**
Women, n (%)		
Age (years), mean (SD)		
Weight (kg), mean (SD)		
Body Mass Index, mean (SD)		
OA in right knee, n (%)		
Duration of knee symptoms, n (%)		
0-6 months		
6-12 months		
1-2 years		
2-5 years		
5-10 years		
More than 10 years		
Radiographic knee OA severity (Kellgren-Lawrence), n (%)		
Grade 1		
Grade 2		
Grade 3		
Grade 4		
Charlson Comorbidity Index, median (iqr)		
Living alone, n (%)		
College education or equivalent, n (%)		
Employment status, n (%)		
Working full-time or part-time		
Sick leave		
Pensioner		
Prior treatment of knee OA, n (%)		
Exercise		
Physiotherapy		
Paracetamol		
NSAIDs		

Cortisone injection		
Surgery		
Menisci with surgery		
Knees with debridement		
Knees with other surgery		
Others		
KOOS scores		
$KOOS_4$		
Pain		
Symptoms		
ADL		
Sport/Rec		
QOL		
EQ-5D, mean (SD)		
EQ-5D Index		
EQ VAS		
Functional performance, mean (SD)		
Time (s) from the Timed Up and Go		
Time (s) from the 20-meter walk test		
Have used pain killers in the last week (n (%))		

8.3. Table 3. Treatment-related variables

Variable	**MEDIC**	**Usual Care**	**P Value**
Compliance with exercise during the 12 weeks, n (%)			
Usage of the other aspects of the treatment program at least every day at the 3month follow-up, n (%)			
Insoles			
Patient education			
Dietary advice			
Satisfied with the treatment effects after 12months			
Surgery during follow-up			
TKA			
Days from randomization, mean (SD)			
Menisci with surgery			
Days from randomization, mean (SD)			
Knees with debridement			
Days from randomization, mean (SD)			
Other surgery			
Days from randomization, mean (SD)			
Total number of surgery			

8.4. Table 4. Outcome at 1 year

Baseline characteristics	**Improvement in MEDIC-group**	**Improvement in Usual Care-group**	**Between-Group difference**
Mean (months) follow-up after start of MEDIC-treatment (95% CI)			
Primary endpoint: mean change in $KOOS_4$ from baseline to 1 yr (95% CI)			
Secondary Endpoints			
Mean change in KOOS subscales score (95% CI)			
Pain			
Symptoms			
ADL			
Sport/Rec			
QOL			
Mean change in time (s) from the Timed Up and Go (95% CI)			
Mean change in time (s) from the 20-meter walk test (95% CI)			
Mean change in EQ-5D (95% CI)			
EQ-5D Index			
EQ VAS			
Mean weight change (kg; 95% CI)			

Change in participants using pain killers in the last week (n (%))			